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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/355,014 | 09/13/1999 | VANESSA HSEI | P1085R3 | 5890 |

25213 7590 03/19/2003

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| EXAMINER |
|---|
| HELMS, LARRY RONALD |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1642 | |

DATE MAILED: 03/19/2003

26

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/355,014 | HSEI ET AL. | |
| | Examiner | Art Unit | |
| | Larry R. Helms | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *07 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1 and 27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

1. Claims 2-4, 8-9, 13, 15, 16, 18, 20-26, 28, 30-34 have been canceled.

Claims 1 and 27 have been amended.

2. Claims 1 and 27 are pending and under examination.

3. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

4. The following Office Action contains some NEW GROUNDS of rejection necessitated by amendment.

### *Rejections Withdrawn*

5. All previous rejections are withdrawn in view of the amendments to the claims.

### *The following are some NEW GROUNDS of rejection*

### *Double Patenting*

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 1 and 27 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 124, 127-128 of copending Application No. 09/489,394 in view of Doerschuk et al (WO 95/23865, published 9/8/95). Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims in the instant application are directed to a conjugate of an antibody which has PEG of at least 20kD or 30kD conjugated to the cysteine residue in the hinge wherein the antibody wherein the apparent molecular weight is at least about 500 kD and the antibody binds to human IL-8. The claims in the 09/489,394 application are directed to the same conjugates that bind other antigens that are therapeutically relevant. It would have been obvious to substitute the antibody that binds other therapeutically relevant antigens with an antibody that binds IL-8 as taught by Doerschuk et al because one would be motivated and had a reasonable expectation of success to substitute the antibody that binds other therapeutically relevant antigens with an antibody that binds IL-8 because Doerschuk et al teach that antibodies to IL-8 are important for the treatment of inflammatory disorders (see abstract and entire document).

This is a provisional obviousness-type double patenting rejection.

Claims 1 and 27 are directed to an invention not patentably distinct from claims 124, 127-128 of commonly assigned 09/489,394. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned 09/489,394, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 CFR 1.78(c) and 35 U.S.C. 132 to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

8. Claims 1 and 27 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 25, 26 of copending Application No. 09/726,258. Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims in the 09/726,258 would anticipate the claims in the instant application. In addition it would be obvious that a conjugate of 500 kD would be at least about 8 fold greater than the antibody fragment

because a Fab is about 50 kD and a conjugate of about 500 kD would be 10 fold greater.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***Claim Rejections - 35 USC § 103***

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Faanes et al (U.S. Patent 5,695,760, filed 4/24/95) and further in view of Zapata et al (FASEB J. 9:A1476, 1995) and Doerschuk et al (WO 95/23865, published 8/95).

The claims recite a conjugate of an antibody which has PEG of at least 20kD or 30kD conjugated to the cysteine residue in the hinge wherein the antibody wherein the apparent molecular weight is at least about 500 kD and the antibody binds to human IL-8.

Faanes et al teach the methods and modifications of antibodies with attachment of PEG molecules to the antigen binding fragments. Faanes et al teach the anti-CD18 antibody (see column 7, lines 50-55) and humanization (column 14, line 40), fragments of the antibody (Fab and F(ab')2) (see column 10, lines 12-13), derivatives of PEG (column 12, lines 19-28), antibodies with biological excipient (column 19, lines 49-57) which are sterile (column 20, line 20), and the antibodies can be modified to contain

about 2-15 molecules of PEG (column 6, lines 21-24) with PEG 5 kD to higher molecular weight PEGs (column 14, lines 9-10) . Faanes et al also teach a method for separating fragments of antibodies from PEG-modified fragments (column 13-14) The method can separate PEG-modified antibody fragments with 1, 2, 3, etc, PEG molecules (column 18, lines 19-34). Faanes et al also teach the determination of the apparent molecular weight of the conjugates using the Stokes radius (column 19, lines 35-41) and teaches an antibody which was modified with PEG has a molecular weight of 540 kD (column 19, lines 35-41). Faanes et al does not teach attachment of PEG to the hinge region of the antibody fragment or that the antibody binds IL-8. These deficiencies are made up for in the teachings of Zapata et al and Doerschuk et al.

Zapata et al teach covalent attachment of MePEG to an antibody fragment of Fab' or F(ab')2 that binds a therapeutically relevant antigen of DC18 through the single free thiol in the hinge region.

Doerschuk et al teach an IL-8 monoclonal antibody that binds human IL-8 (see page 2, lines 14-19).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a conjugate comprising an antigen binding fragment with PEG attached in the hinge region as taught by Zapata et al and producing a conjugate with the claimed characteristics as taught by Faanes et al that binds IL-8 as taught by Doerschuk et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a conjugate comprising an antigen binding fragment with PEG attached in the hinge region as taught by Zapata et al and producing a conjugate with the claimed characteristics as taught by Faanes et al that binds IL-8 as taught by Doerschuk et al because Zapata et al teach the "humanized

anti-CD18 Fab' fragment, which contains a single free thiol, was expressed in E. Coli and recovered in high yield". In addition, Zapata et al teach "modification of the anti-CD18 Fab' with either size of MePEG maleimide did not alter the ability of this molecule to bind antigen". In addition, Zapata et al teach that the pharmacokinetic data show that the MePEG-Fab' species had reduced clearance as compared to the native Fab' and because Zapata et al teach MePEG was used to selectively modify the single free thiol of the Fab' polypeptide in a rapid and efficient reaction.". In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a conjugate comprising an antigen binding fragment with PEG attached in the hinge region as taught by Zapata et al and producing a conjugate with the claimed characteristics as taught by Faanes et al that binds IL-8 as taught by Doerschuk et al because Faanes et al clearly teaches mPEG of up to 40 kD may alternatively be employed (see column 12, lines 61-63) and in view of Zapata et al's teaching that a higher molecular weight (as admitted by applicants) led to extended serum half life, therefore it would be obvious to use a higher MW PEG and as such in view of Faanes et al which teaches 40Kd one skiil in the art would use a higher MW to get reduced clearance and as such this would increase the apparent MW of the conjugate. In addition, it would have been obvious to substitute any therapeutically relavent antibody such as the anti-IL-8 antibody of Doerschuk et al for the antibodies of Zapata et al because Zapata teaches that the antigen binding properties of the antibody were not affected and attachment of PEG to the antibody increases the potential therapeutic value of the molecule.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

11. Claims 1 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zapata et al. (FASEB J. 1995, Abstract #1288, 9:A1479, IDS #19) in view of Braxton (US Pat. No. 5,766,897, IDS #19) and further in view of Doerschuk et al (WO 95/23865, published 9/95, IDS #19).

The claims have been described supra.

Zapata has been described supra. Zapata et al does not teach at least 20 kD PEG or an antibody binding to IL-8. Theses deficiencies are made up for in the teachings of Braxton and Doerschuk et al.

Braxton teach methods for the PEGylation of proteins by attaching a PEG molecule via the thiol group on a free cysteine (see entire document, e.g., column 12 especially lines 48-50). Braxton teach that the molecular weight of the attached PEG may be from 200 to 20,000 MW (i.e., from about 0.2 to 20 kD) and that particularly for relatively small proteins that generally have short half lives and because of their small size have fewer PEG sites available, the PEG moiety used should be of a higher molecular weight (see especially lines 48-65).

Doerschuk et al has been described supra.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention by substituting the anti-IL-8 Fab' fragments of Doerschuk et al. for the anti-CD18 Fab' conjugate taught by Zapata et al. in view of Braxton. One of ordinary skill in the art would have been motivated to add PEG to an anti-IL-8 Fab' fragment using the method of Zapata et al. and Braxton because Doerschuk et al. teach the usefulness of anti-IL-8 monoclonal antibody Fab'

fragments in treatment and diagnosis of inflammatory disorders and because both Zapata et al. and Braxton teach that addition of PEG reduces serum clearance of therapeutics and reduces immunogenicity. Given the availability of the anti-IL-8 Fab' fragment and the methods of adding PEG, including a 20kD single chain PEG to an antibody Fab' fragment, the ordinary artisan at the time the invention was made would have had a reasonable expectation of producing the instant invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

***Conclusions***

12. No Claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

14. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879